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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/978,637	11/25/97	RABBANI	E- ENZ-53 (DIV5)

RONALD C FEDUS
ENZO DIAGNOSTICS INC
ENZO BIOCHEM INC
527 MADISON AVENUE 9TH FLOOR
NEW YORK NY 10022

HM12/0217

EXAMINER

SCHMIDT, M

ART UNIT

PAPER NUMBER

1635

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**Please find below and/or attached an Office communication concerning this application or
proceeding.**

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/978,637

Applicant(s)

Rabbani et al.

Examiner

Schmidt

Group Art Unit

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—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P r i d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disp sition of Claims

- ☒ Claim(s) 2-24 and 245-313 is/are pending in the application.
Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 2-24 and 245-313 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☒ Notice of Reference(s) Cited, PTO-892
- ☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other _____

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DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures: Sequences in this specification and/or the claims are not referenced by sequence identifiers.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3. Claims 2-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2-24 of copending Application Nos.: 08/978,632, 08/978,633, 08/978,634, 08/978,635, 08/978,636, 08/978,638, 08/978,639, and 08/574,443. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

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Claim Rejections - 35 USC § 112

4. Claims 2-21 and 265 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-21 are indefinite because they depend from canceled claim 1. Therefore, claims 2-21 do not depend on any independent claim.

Claim 265 contains the redundant language “localizing localizing entity”

5. Claims 2-21 and 245-313 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The constructs taught in the claims 2-24 are broadly drawn to a multitude of possible nucleic acid based constructs for use in a cell to produce a product (and in any context, *in vivo* or *in vitro*), comprising: (1) the construct as linear or circular, (2) the construct as comprising 1,2 or 3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5) containing chemically-modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net charge, (8) the construct imparting a “further biological activity” by the modified nucleotide,

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analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim 1, further described as attached to a "segment" or "tail" of the construct, and further defined as being a macromolecule or small molecule or combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

Claims 245-264 are drawn to nucleic acid compositions and cells containing them. Specifically, a composition for producing a primary, secondary and tertiary nucleic acid component independently obtained in the cell. The limitations further are drawn to a signal processing sequence in the composition such as a promoter, initiator, terminator, intron or cellular localization element. Claims 265-289 are drawn to compositions comprised of a nucleic acid component and producing in a cell a non-natural nucleic acid product further comprising a portion of a localizing entity, and cells and organisms for use in. The limitations of the dependent claims are further drawn to nuclear localized RNA comprising snRNA such as U1 or U2. Claims 290-298 are drawn to a process for localizing the above claimed composition in claims 265-289. Claims 299-313 are drawn to a nucleic acid component capable of producing more than one non-homologous nucleic acid sequence in a cell complementary to a target nucleic acid or protein. The dependent limitations include use of a localizing protein (claim 310).

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The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7

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polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the “A” antisense T7 operon , the “B” antisense T7 operon and the “C” antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs (“various U1 constructs described above” p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture.

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Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to a complementary polynucleotide sequence. The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed. The

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specification fails to provide guidance for the breadth claimed since the claims vaguely claim “constructs” which “produce products.” The specification teaches only by way of example HIV inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Claims 245-313 are further drawn to a broad genus of constructs and processes of using such constructs in cells. The language of claim 245 reads on vector replication in a cell, and expression of any gene which is then modified (spliced, etc.) so that a third nucleic acid sequence is produced, or acts on another nucleic acid sequence such as a ribozyme to cleave the product. The language of claim 265 and 290 reads on *any* construct and process for production of a recombinant nucleic acid in a cell having a localizing entity, for example to localize the expressed sequence to its target region. The language of claim 299 reads on any construct for production of nucleic acid sequences in a cell which target another nucleic acid sequence or protein in the cell.

The scope of genus sought for such constructs is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims nebulously claim “construct” which produce “products” having general characteristics of a huge genus of recombinantly expressed nucleic acid products in a cell of interest. The specification does not teach compositions producing primary, secondary, tertiary (or the production of more than one sequence as in claim 299) constructs, other than the triple U1 construct having a cassette structure. The only localizing entity shown by way of example in the specification is the use of the U1 sequence for direction of the antisense sequences

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to the nucleus. The specification teaches only prophetically constructs capable of binding to a specific protein of interest in the cell, and by way of example, only vectors such as the U1A,B,C construct for expression of antisense to HIV in cells.

Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach “although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1).”

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by “raising the temperature or changing the ionic strength, manipulations that are commonly used to

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reduce background binding in nucleic acid hybridization experiments.” (Branch, p. 48) Discovery of antisense molecules with “enhanced specificity” *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it “is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49).” And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of “trial and error” experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

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No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend. Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

6. Claims 2-24, 245-289 and 299-313 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product in a cell. Claims 245-289 and 299-313 are drawn to a broad scope of (1) compositions for production of primary, secondary and tertiary nucleic acid products in a cell, (2) nucleic acid compositions comprising localizing entities, and (3) nucleic acid compositions for producing a sequence homologous to an endogenous cell sequence or protein.

The claims broadly encompass "constructs" for producing a "product" and it is not clear what is embraced by the claims. The claims 22-24 read on vectors, genomes, cell processes like translation, transcription, etc. Furthermore, the scope of "chemical modification" as used in claim 22 is not clear in relation to the construct. Claims 245-289 and 299-313 read on vector replication in a cell, expression of any recombinant gene with a signal sequence or any such sequence that

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A.C.C.

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would direct it to a specific location or any sequence to target another nucleic acid or protein in the cell.

The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.

Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 245-289 and 299-313, the only localizing entity taught is use of the U1 gene with an internal antisense sequence for localization of the antisense to the nucleus once expressed in the cell. Further, the only primary, secondary, and tertiary product producing construct described in the specification is the cassette structured 'triple U1' construct and with the use of intron sequences the control of processing of the T7 polymerase taught.

Furthermore, the actual constructs used in the HIV challenge and Lac-Z assays taught in the specification are not described in clear and exact terms (p. 169, line 3 recites "U1 clone"; p. 169, para. © line 1 recites "triple U1 construct"; and p. 167, last line recites "various U1 constructs described above") and it is not clear whether the constructs used had the intron sequence in the T7 polymerase, or even which constructs were used in the assays.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the

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specification for such a broad genus of possible “constructs,” coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of “construct” species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112 “Written Description” requirement.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al..

The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ionically to an entity comprising a modification or a ligand, and further comprises a hybridized polynucleotide tail.

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Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

9. Claims 265-298 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al..

The claimed invention is drawn to construct and methods of use of a construct for production of a non-naturally occurring nucleic acid product in a cell comprising a portion of a localizing entity in a cell.

Sullenger et al. teaches, for example, nucleic acid constructs for production in a cell of ribozyme sequences tethered to a localization signals. Although Sullenger does not specifically teach snRNA, U1 or U2, localization signals, many other nuclear localization signals are taught as having improved specificity to the particular target site of interest (his examples are also drawn to HIV targets). Sullenger et al. also encompass use of protein binding nucleic acid sequences.

10. Claims 245-249, 251, 255, 258-261, and 264 are rejected under 35 U.S.C. 102(b) as being anticipated by Huse et al..

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The claimed invention is drawn to a composition comprising a primary nucleic acid component which upon introduction into a cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, wherein the primary nucleic acid component is not obtained with the secondary or tertiary component.

Huse et al. teach the Lambda ZAP vector known in the art for expression of a second vector after transformation into the cell having the potential to subsequently express a product. Claim 245 as written, however, would literally read on any generic propagating vector in a cell.

11. Claims 245-264 and 299-313 are rejected under 35 U.S.C. 102(e) as being anticipated by Giri et al.

Claim 245 is drawn to a composition comprising a primary nucleic acid component which upon introduction into a cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, wherein the primary nucleic acid component is not obtained with the secondary or tertiary component. Claim 299 is drawn to nucleic acid construct which when in a cell produces more than one non-homologous nucleic acid sequence with complementarity to a target nucleic acid or protein.

Giri et al. teach a eukaryotic expression vector for simultaneous expression of a sense and an antisense sequence from different promoters (see column 3). Targeting different viral sequences (protein or nucleic acid) is within the scope of the vectors as taught.

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12. Claims 245-313 are rejected under 35 U.S.C. 102(b) as being anticipated by DeYoung et al..

The claimed invention is drawn to: (1) compositions for production of primary, secondary and tertiary nucleic acid products in a cell, (2)nucleic acid compositions comprising localizing entities, and (3)nucleic acid compositions for producing a sequence homologous to an endogenous cell sequence or protein.

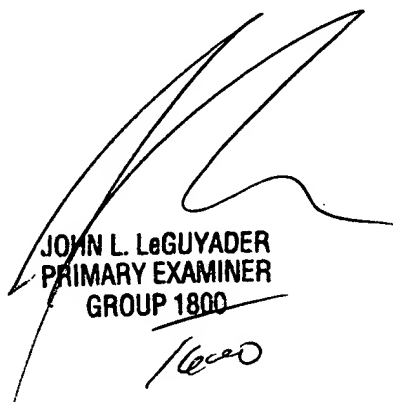
DeYoung et al. teach expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. The U1 sequence is a known localizing sequence to the cell nucleus. The production of ribozymes from the construct taught by DeYoung reads on the broad genus of constructs for production of secondary and tertiary nucleic acid products and compositions for producing a sequence homologous to an endogenous cell sequence.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800